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Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma

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With recent remarkable technological advances in radiation therapy, stereotactic body radiation therapy (SBRT) is regarded as an alternative treatment option for hepatocellular carcinoma (HCC) that is not suitable for curative treatment. Several prospective and retrospective studies on the use of SBRT in patients with HCC showed promising results. Furthermore, on-going prospective studies are examining the role of SBRT as a single ablative modality or a combination treatment in patients with HCC. Here, we summarize previous studies and recent updates and discuss the future perspectives of SBRT for HCC. (*J Liver Cancer* 2018;18:94-102)

Keywords: Carcinoma, Hepatocellular; Radiation

INTRODUCTION

With remarkable recent technological advances in radiation therapy, including four-dimensional computed tomography, intensity-modulated radiation therapy, image-guided radiation therapy (IGRT), and respiratory-gated delivery, stereotactic body radiation therapy (SBRT) has been regarded as an alternative treatment option for small hepatocellular carcinomas (HCCs) that are not suitable for hepatic resection and radiofrequency ablation (RFA).¹⁻⁴ Recently, 2018 practice guidance by the American Association for the Study

of Liver Disease suggested SBRT as one of alternative treatments to thermal ablation for the Barcelona Clinic Liver Cancer stage A patients.⁵ Here, we summarize previous studies and recent updates and discuss the future perspectives of SBRT for HCC.

DEFINITION OF SBRT

SBRT (also known as stereotactic ablative body radiation therapy [SABR]) is an external beam radiation therapy method used to deliver a high dose of radiation very precisely to an extracranial tumor, using a small number of fractions.⁶ The ability to deliver a few fractions of high-dose radiation with high targeting accuracy and rapid dose fall-off gradients outside the target region provides the basis for the development of SBRT.⁷

However, HCC presents challenges in imaging at simulation and at beam delivery because of the lack of inherent

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contrast between the tumor and surrounding liver and respiratory motion.⁸ Because a normal liver itself as well as many critical normal organs surrounding the liver are radiosensitive, a comprehensive image guidance and motion management strategy are necessary to ensure safe and effective positioning for treatment.⁹ Therefore, SBRT practice, especially for HCC, requires a high level of confidence in terms of accuracy of the entire treatment procedure, and this confidence is achieved through the integration of modern imaging, simulation, treatment planning, and delivery technologies in all phases of the radiation therapy process.¹⁰ On the contrary, SBRT is not recommended if the extent of the tumor is uncertain or if large volumes of normal tissues need to be included within the radiation field to ensure sufficient coverage of microscopic tumor infiltration.³

RESULTS OF PROSPECTIVE STUDIES

Several prospective studies on the use of SBRT in patients with HCC have been reported. Although the indications for SBRT vary among studies, most have shown promising results after SBRT for HCC (Table 1).

Tse et al.¹¹ conducted a phase I study of SBRT for unresectable HCC (n=31) or intrahepatic cholangiocarcinoma (n=10) not suitable for standard therapies, and they reported a 1-year in-field local control rate of 65% and a median survival of 11.7 months for HCC. In the expanded phase I/II trial at the same institution, Bujold et al.¹² reported a 1-year local control rate of 87% and a median overall survival of 17 months. In these two studies, an individualized six-fraction SBRT allowed large, multifocal tumors and HCC with major vascular thrombosis to be treated as opposed to most SBRT focusing on small HCC in other series.¹² Nevertheless, SBRT can lead to sustained local control with a low incidence of serious toxicity in patients for whom curative local treatment options are not available. In another phase I/II study from North America, the authors reported 2-year local control and overall survival rates of 90% and 67%, respectively, and a median time-to-progression of 47.8 months in 60 patients with liver-confined HCC (median tumor diameter, 3.2 cm) at the time of SBRT.¹³

Similarly, recent prospective trials conducted in Asian countries have also reported excellent clinical outcomes with SBRT for HCC. Kang et al.¹⁴ conducted a phase II trial of SBRT as a local salvage treatment after incomplete transarterial chemoembolization (TACE) in patients with HCC. They included single or multiple lesions, even with vascular invasion, and a maximum tumor diameter of <10 cm for salvage SBRT; they reported a 2-year local control rate of 94.6% in patients with incomplete TACE for inoperable HCC.¹⁴ Takeda et al.¹⁵ also conducted a phase II study of SBRT for early stage or small HCC with curative intent. Among the included patients, 32 (36%) were treatment naïve and 18 had HCC that measured ≥3 cm at its greatest dimension (maximum tumor dimension, ≥4 cm). They also reported a 3-year local control rate of 96.3% and a 3-year liver-related cause-specific survival rate of 72.5% and concluded that SBRT achieved high local control and overall survival rates for patients with solitary HCC in treatment-naïve, intrahepatic failure, residual disease, and recurrent settings.¹⁵

One recent phase II study revealed that patients who underwent individualized adaptive therapy, i.e., patients received 3 of 5 planned SBRT treatments, waited 4 weeks for potential subclinical liver function change and then underwent repeat assessment of the indocyanine green 15, and the radiation dose for the final 2 treatments was then adjusted. This approach can be used to achieve both high rates of local control (2-year local control rates of 95%) and a high degree of safety.¹⁶

RETROSPECTIVE STUDY RESULTS

In addition to early phase prospective trials, many retrospective studies have examined SBRT for HCC, and studies involving >50 patients are summarized in Table 1. Jang et al.¹⁷ reported a dose-response relationship in 108 patients (122 lesions) with HCC who were treated with 3-fraction SBRT. The median longest tumor diameter was 3 cm (range, 1-7 cm), and the median prescribed dose was 51 Gy (range, 33-60 Gy). They divided the dose group as follows: >54 Gy, 45-54 Gy, and <45 Gy and reported 2-year local control rates of 100%, 78%, and 64%, respectively ($P=0.009$).¹⁷ In contrast,

Table 1. Summary of the recent prospective and retrospective (with >50 patients) studies on SBRT for HCC

Study	Design	No. of pts.	Clinical condition & indication				Dose prescription, median (range), Gy/fractions	LC (%)	OS (%)
			No. of HCC	PVTT	Extrahepatic	Tumor size, median (range) (cm)			
Tse et al ¹¹ (2008)	Phase I	31	1	Yes, 52%	Yes, 9%	173 mL (9-1,913 mL)	A	65 (1 Y) (HCC+CC)	48 (1 Y)
Andolino et al ¹³ (2011)	Phase I/II	60	1-3	NA	No	3.1 (1.0-6.5)	A, B	CP-A: 44/3 (30-48) CP-B: 40/5 (24-48)	67 (2 Y)
Kang et al ¹⁴ (2012)	Phase II	47	1-3	Yes, 11%	No	2.9 (1.3-7.8) (sum of size)	A, B7	57/3 (42-60/3)	69 (2 Y)
Bujold et al ¹² (2013)	Phase I/II	102	NA	Yes, 55%	Yes, 12%	7.2 (1.4-23.1)	A	24-54/6	55 (1 Y)
Takeda et al ¹⁵ (2016)	Phase II	90	1	NA	No	2.3 (1.0-4.0)	A, B8	35/5 or 40/5	67 (3 Y)
Feng et al ¹⁶ (2017)	Phase II	69	1-4	Yes, 18% (HCC+CC+metastasis)	NA	3 (0-13.0) (all)	A, B9 (HCC+CC+metastasis)	49 (23-60/3-5) (HCC+CC+metastasis)	NA
Yoon et al ¹⁹ (2013) & Jung et al ²⁹ (2013)	Retro	93	1-2	No	No	2 (1.0-6.0)	A, B	45/3 (30-60/3-4)	86 (1 Y) 54 (3 Y)
Jang et al ¹⁷ (2013)	Retro	82	1-3	Yes, 10%	NA	3.0 (1.0-7.0)	A, B7	51/3 (33-60/3)	63 (2 Y)
Bibault et al ²⁰ (2013)	Retro	75	1-3	NA	No	3.7 (3.0-4.4)	A, B8	45/3 (24-45/3)	79 (1 Y) 50 (2 Y)
Yamashita et al ³² (2014)	Retro	79	1	NA	NA	2.7 (0.6-7.0)	A, B, C	48/4 (40-60/4-10)	53 (2 Y)
Sanuki et al ¹⁸ (2014)	Retro	185	1	NA	No	35 Gy group: 2.7 (1.0-5.0) 40 Gy group: 2.4 (0.5-5.0)	A, B	CP-A: 40/5 CP-B: 35/5	95 (1 Y) 70 (3 Y)
Takeda et al ³³ (2014)	Retro	63	1	NA	No	2.6 (1.0-5.0)	A, B	CP-A: 40/5 CP-B: 35/5	100 (1 Y) 73 (3 Y)
Wahl et al ²⁵ (2015)	Retro	63	1-4	NA	NA	2.2 (0-10)	A, B, C10	30 or 50 (27-60/3 or 5) 84 (2 Y)	74 (1 Y) 46 (2 Y)
Huertas et al ²² (2015)	Retro	77	1-3	NA	No	2.4 (0.7-6.3)	A, B8	45/3	99 (1 Y) 57 (2 Y)
Su ²³ et al (2015)	Retro	132	NA	NA	NA	3.0 (1.1-5.0)	A, B	42-46/3-5, 28-30/1	91 (1 Y) 74 (3 Y) 64 (5 Y)
Kimura et al ²¹ (2015) & Kubo et al ³⁴ (2017)	Retro	65	1-2	No	No	1.6 (0.5-5.4)	A, B	48/4	100 (3 Y) 100 (5 Y)
Lo et al ³⁵ (2017)	Retro	89	NA	Yes, 49%	Yes, 29%	6.2 (1.2-18.5)	A, B	45 (25-60/4-6)	78 (3 Y) 46 (1 Y) 24 (3 Y) 10 (5 Y)
Jeong et al ²⁴ (2018)	Retro	119	NA	No	No	1.7 (0.8-6.0)	A, B	45/3 (30-60/3-4)	99 (1 Y) 97 (3 Y)

SBRT, stereotactic body radiation therapy; pts, patients; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombus; CP, Child-Pugh; Gy, Gray; LC, local control; OS, overall survival; Y, year; CC, cholangiocarcinoma; NA, not available; Retro, retrospective.

Sanuki et al.¹⁸ evaluated local control rates according to two different prescription dose schedules in relatively large numbers of patients. In their analysis, they restricted the maximum tumor size to ≥ 5 cm (range, 0.8-5 cm) and reported no difference in 3-year local control rates between the two groups (91% in the 35 Gy/5-fraction group vs. 89% in the 40 Gy/5-fraction group, $P=0.99$).¹⁸ Because both prescribed dose and tumor size can affect the local control rate after SBRT, a more well-designed study is required to determine the optimal prescribed dose to maximize tumor control without increasing the risks for hepatic toxicity following high-dose radiation therapy.

Other recent retrospective studies revealed that SBRT for small HCC can yield excellent local control rates (range, 84.1-100%) and favorable overall survival outcomes (range,

50.4-81.9% at 2 years).¹⁹⁻²³ However, SBRT has been used as a salvage treatment following various locoregional treatments in most previously reported studies; therefore, it is difficult to directly compare overall survival rates between SBRT and other curative treatments, such as hepatic resection or RFA.¹⁹ Jeong et al.²⁴ recently published excellent local control and overall survival rates (97.0% and 83.8% at 3 years, respectively) using a highly sophisticated radiation therapy technique, including IGRT. Therefore, evolution in radiation therapy techniques can also contribute to better clinical outcomes in the management of small HCC.

Wahl et al.²⁵ conducted a retrospective comparison study between RFA ($n=161$) and SBRT ($n=63$) for inoperable and non-metastatic HCC from 2004 to 2012. They reported no significant difference of freedom from local progression be-

Figure 1. An example of good response of HCC after SBRT. The patient who had a 1.8 cm HCC in segment II (A: arterial phase, B: portal phase) received 45 Gy in three fractions of SBRT (C, D). This tumor disappeared on follow-up CT images with the background radiation-induced parenchymal change around the tumor at 3 months after SBRT (E: arterial phase, F: portal phase). HCC, hepatocellular carcinoma; SBRT, stereotactic body radiation therapy; Gy, Gray; CT, computed tomography.

Table 2. Summary of dose constraints for SBRT and treatment-related toxicities

Study	Constraints		Toxicity		
	Upper GI	Liver	Liver	GI	Others (rib, biliary, ...)
Tse et al ¹¹ (2008)	0.5 mL of esophagus, stomach, duodenum, or bowel <30 Gy	Normal liver >800 mL	RILD G3: 26% CP class change A→B: 16%	Tumor-duodenal connection: 3%	Right-sided pleural effusion: 10%
Andolino et al ¹³ (2011)	D_{max} of small bowel <12 Gy	CP-A: 1/3 of normal liver ≤10 Gy; rV_7 ≥500 mL CP-B: 1/3 of normal liver ≤18 Gy; $rV_{12, Gy}$ ≥500 mL	CP class change: 20% (A→B: 12%, B→A: 8%) Hepatic failure: 7% (all with a CP score ≥8)	No GI toxicity ≥G3	No other toxicity ≥G3
Kang et al ¹⁴ (2012)	GI constraints were not considered	$rV_{17, Gy}$ >700 mL	No RILD CP class change A→B: 13%	GI toxicity G3: 6% Gastric ulcer G4: 4%	NA
Bujold et al ¹² (2013)	D_{max} of stomach, duodenum, small bowel, and large bowel <32, 33, 34, and 36 Gy	Normal liver >700 mL	RILD G3: 11% Worsening of CP class: 29% G5 hepatic failure: 3%	Duodenal bleeding G5: 1%	Cholangitis G5: 1% (HCC invaded common BD)
Takeda et al ¹⁵ (2016)	Stomach, bowel <25 Gy	$V_{20, Gy}$ <20% of normal liver	RILD G3: 2% Worsening of CP score ≥2: 9%	No GI toxicity	NA
Feng et al ¹⁶ (2017)	0.55 mL of stomach, duodenum <27.5 Gy, 30 Gy	ICGR15 <44%	Worsening of CP score ≥2: 8% (HCC+CC)	Duodenal bleeding G3: 1% (HCC+CC)	NA
Yoon et al ¹⁹ (2013) & Jung et al ²⁹ (2013)	>2 cm from stomach, duodenum; 2 mL of stomach or duodenum <18 Gy; 2 mL of esophagus or large bowel <21 Gy	Normal liver >700 mL, $rV_{15, Gy}$ >700 mL, mean dose of normal liver <13 Gy	RILD ≥G2: 18% (≥G3: 7%) Worsening of CP score ≥2: 10%	No bleeding or perforation	Rib fracture: 2% BD stricture: 1% (central located tumor)
Jang et al ¹⁷ (2013)	Esophagus: D_{max} <24 Gy; other GI constraints were not considered	$rV_{17, Gy}$ >700 mL	RILD: 5%	Gastroduodenal ulcer: 2% perforation: 2%; colonic ulcer: 1%	Soft tissue toxicity G3: 1%
Bibault et al ²⁰ (2013)	0.5 mL of stomach, duodenum, small intestine <25 Gy, 24 Gy, 27 Gy	$rV_{17, Gy}$ >700 mL, $V_{15, Gy}$ <50%, $V_{21, Gy}$ <33%	Liver decompensated ascites: 7%	Gastric ulcer G4: 1%; Duodenal ulcer G2: 4%	NA
Sanuki et al ¹⁸ (2014)	Bowel <25 Gy	$V_{20, Gy}$ <20% of normal liver	Worsening of CP score ≥2: 10% G5 hepatic failure: 1%	NA	NA
Takeda et al ³³ (2014)	>2 cm from GI tract	$V_{20, Gy}$ <20% of normal liver	RILD G3: 2%	No GI toxicity	No other toxicity
Wahl et al ²⁵ (2015)	0.5 mL of stomach, duodenum <22.5 Gy, 24 Gy	NA	RILD: 2%	GI toxicity ≥late G3: 8.3%	biliary toxicity ≥late G3: 3%
Huertas et al ²² (2015)	Stomach: D_{max} <24 Gy, $D_{5, mL}$ <21Gy; Duodenum: D_{max} <24 Gy, $V_{15, Gy}$ <5 mL	$D_{33\%}$ <21 Gy, $D_{50\%}$ <15 Gy	RILD: 5%	Gastric ulcer G3: 1%, G4: 1%; Colic ulcer G2: 1%	Rib pain: 1%
Su et al ²³ (2015)	1 mL of duodenum and stomach <25 Gy/3-5 fx, <15 Gy/1 fx	3-5 fx: $rV_{15, Gy}$ >700 mL, $V_{15, Gy}$ <1/3 total liver volume 1 fx: $rV_{10, Gy}$ >700 mL, $V_{10, Gy}$ <1/3 total liver volume	G5 hepatic failure: 3% Hepatic encephalopathy ≥G3: 2%	Upper GI hemorrhage ≥G3: 3%	NA
Kimura et al ²¹ (2015) & Kubo et al ³⁴ (2017)	21 mL of GI tract <30 Gy/4 fx	NA	RILD G3: 12%	No ≥G3	BD stricture G2: 2% (G3: 0%)
Lo et al ¹⁵ (2017)	NA	Normal liver >700 mL	RILD: 11%, fatal RILD: 2% Worsening of CP score ≥2: 13%	Gastric ulcer G3: 2%	NA
Jeong et al ²⁴ (2018)	>2 cm from stomach, duodenum; 2 mL of stomach or duodenum <18 Gy; 2 mL of esophagus or large bowel <21 Gy	Normal liver >700 mL, $rV_{15, Gy}$ >700 mL, mean dose of normal liver <13 Gy	RILD ≥G2: 8% (G3: 2%) Worsening of CP score ≥2: 6%	No bleeding or perforation	Rib fracture: 8% BD stricture G3: 2%

GI, gastrointestinal; Gy, Gray; RILD, radiation-induced liver disease; CP, Child-Pugh; D_{max} , maximum dose; $rV_{10, Gy}$, total volume-volume receiving certain of b Gy; G, grade; NA, not available; HCC, hepatocellular carcinoma; BD, bile duct; $V_{d, Gy}$, volume receiving certain of a Gy; ICGR, indocyanine green retention rate; CC, cholangiocarcinoma; fx, fraction.

tween the two modalities, however, SBRT was associated with improved local control compared with RFA for HCC ≥ 2 cm. Although both treatment modalities are complementary to each other according to tumor location and accessibility, SBRT can also play a role as an ablative treatment option in the management of HCC.²⁵ Fig. 1 shows a representative case of HCC who achieved complete response after SBRT.

SBRT-RELATED TOXICITY

1. Hepatic toxicity

Radiation-induced hepatic toxicity can occur after SBRT because the normal liver is a radiosensitive organ. Because most HCCs occur with a background of chronic liver disease, including viral hepatitis, non-classic radiation-induced liver

disease (RILD) (elevation in liver transaminases or worsening of Child-Pugh score by ≥ 2) usually occurs within 3 months after completion of SBRT in the absence of classic RILD (elevated alkaline phosphatase level).²⁶ The incidence of hepatic toxicity varies between studies (range, 2-13%) using different dose constraints for normal liver (Table 2). However, most patients showed improved or stable hepatic function with supportive care during the follow-up period, and the occurrence of fatal hepatic toxicities after SBRT is rare. According to baseline liver function before SBRT, the incidence of hepatic toxicity could increase in patients with Child-Pugh class B hepatic function;²⁷⁻³⁰ therefore, a more conservative dose prescription may be required for patients with liver function of Child-Pugh class B.

Figure 2. Examples of complications following SBRT: (A) biliary stricture at 13 months after SBRT; (B) rib fracture at 19 months after SBRT; (C) radiation pneumonitis at 6 months after SBRT. SBRT, stereotactic body radiation therapy.

2. Gastrointestinal toxicity

Gastrointestinal luminal structures, such as the stomach, duodenum, or large bowel are also radiosensitive organs in SBRT for HCC, if the tumor is located adjacent to these organs. Despite more accurate targeting ability using recently advanced radiation therapy technology, a sufficient safety margin between the tumor and these gastrointestinal structures remain necessary to reduce serious complications, including bleeding or perforation. According to the previous studies, the overall incidence of gastrointestinal toxicity is relatively low (range, 0-8.3%) (Table 2); nonetheless, most toxicities are severe and required recovery in intensive care. Because most patients have underlying liver cirrhosis, portal hypertension, and coagulopathy that can exacerbate the risk for gastrointestinal toxicities, care should be taken to review the proximity to critical normal organs that are highly sensitive to radiation prior to considering SBRT for HCC.

3. Other toxicity

The most frequent constitutional symptoms related to SBRT are fatigue, anorexia, and nausea; however, most

symptoms are mild and recovered well without additional supportive care. If a tumor is in a central area, there is a chance to develop biliary stricture owing to hepatic fibrosis after SBRT. However, the incidence of this complication is also very low (2-3%). Radiation pneumonitis can occur in the right lower lung field if HCC is located near the diaphragm; however, most observed as radiographic changes with no accompanying symptoms. Some patients experience rib fractures or soft tissue toxicities after SBRT for peripheral tumors; nevertheless, most patients do not require any specific treatment (Table 2). Fig. 2 shows representative cases of biliary stricture, rib fracture, and radiation pneumonitis following SBRT.

ON-GOING CLINICAL TRIALS

There are many on-going prospective, single-arm, phase I or II studies regarding the role of SBRT in patients with HCC.³¹ In these trials, SBRT is used as a single ablative modality or as a combination treatment with TACE or systemic therapies. Moreover, there are many prospective randomized trials that aim to compare SBRT with other modalities or to define the use of SBRT in combination with other treatment

Table 3. On-going randomized trials

Trial identifier	Patient population	Modalities	Primary outcome
NCT03172559	Bridge to liver transplant in HCC	SBRT vs. no intervention	Proportion of participants that get to be transplanted
NCT02182687	Bridge to liver transplant in HCC	SBRT vs. TACE	Time to first additional intervention to the treated lesions
NCT01963429	Recurrent small HCC	PBT vs. RFA	Local progression free survival
NCT02323360	Incomplete TACE	SBRT vs. TACE	Local tumor control
NCT03338647	Advanced HCC	SBRT vs. TACE	Progression (total of local, intra- and extrahepatic)
NCT01730937	Advanced or recurrent HCC	Sorafenib +/- SBRT	Overall survival
NCT03168152	Localized HCC	SBRT vs. MWA	Time to local tumor progression
NCT02470533	HCC ineligible for surgery or RFA	SBRT vs. DEB-TACE	Time to progression
NCT02762266	Residual or recurrent HCC after TACE	SBRT vs. TACE	Freedom from local progression
NCT03079778	HCC ineligible for surgery	TACE +/- SBRT	Time-to-intrahepatic-progression
NCT02794337	Unresectable HCC	DEB-TACE +/- SBRT	In-field progression free survival

HCC, hepatocellular carcinoma; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; PBT, proton beam therapy; RFA, radiofrequency ablation; MWA, microwave ablation; DEB, drug-eluting beads.

(Table 3). All these results are likely to provide more reliable answers on the use of SBRT in the management of HCC.

CONCLUSIONS

Based on results of early phase trials and retrospective series, SBRT is a safe and effective treatment modality for patients with HCC. SBRT can be a good alternative treatment for patients with small HCCs that are unsuitable for hepatic resection or local ablative therapy. A more definite role for SBRT in HCC may be identified from results of on-going prospective trials.

AUTHOR CONTRIBUTIONS

J Jung and SM Yoon are responsible for the acquisition of the data and drafting of the manuscript.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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